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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,933	09/14/2005	Tong Shangguan	TRA-027.01	1561

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,933	SHANGGUAN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,11,13-34,36-69,71-80,84-107,109-142,144-151 and 153-168* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,11,13-34,36-69,71-80,84-107,109-142,144-151 and 153-168* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/16/09 has been entered.

Claims 8, 9, 12, 81-83, 86, and 108 were canceled.

Claims 1-7, 10, 11, 13-34, 36-69, 71-80, 84-107, 109-142, 144-151, and 153-168 remain pending and are under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 10, 11, 13-17, 25-27, 29-31, 33, 34, 36-69, 71-80, 84-91, 99, 100, 102-104, 106, 107, 109-142, 144-147, and 153-168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos et al (US Patent 4,235,871), in view of Kikuchi et al (US 4,687,661), Meers et al (US Patent 6,120,797), Lenk et al (US Patent 5,169,637), and Thierry (US 6,096,335).

Papahadjopoulos taught a variety of liposomes comprising nucleic acids such as DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68 column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine (PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. PS is a fusogenic lipid. The liposomes were from 200-400 nanometers in size (column 6, lines 11-14).

Papahadjopoulos taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert solvent to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30.

Regarding claim 89, Papahadjopoulos taught addition of an aqueous solvent to the gel, rather than addition of the gel to an aqueous solvent, but this detail is considered to be a simple matter of design choice, and is therefore an obvious variant of the method of Papahadjopoulos.

Regarding claims 111-122 and 146, Papahadjopoulos is silent as to the total amount of lipid forming and fusogenic lipid expressed as a weight-percent of the gel, but the amounts of these lipids are considered to be result-effective variables that are obvious to optimize in order to modulate the characteristics of the resultant liposomes. See e.g. column 4, lines 53-58; and column 6, lines 11-18 and 28-34.

Regarding claims 124-135, Papahadjopoulos is silent as to the ratio of the weight

of the increment of aqueous medium that can be used to wash the gel, and the weight of the gel itself. However, this is a parameter that would be routinely optimized by one of ordinary skill, see e.g. column 4, lines 53-58.

Regarding claims 136-140, Papahadjopoulos is silent as to the total amount of nucleic acid expressed as a weight-percent of the gel, but the amounts of the nucleic acid is clearly a result-effective variable that is routinely optimized by one of ordinary skill. in order to modulate the characteristics of the resultant liposomes. See e.g. column 6, lines 11-18 and 28-34.

Instant claim 145 requires that the gel or gel particles lack a hydrating agent, and that no hydrating agent is used in step A of the method. The specification defines a hydrating agent at paragraph 74 as a compound having at least two ionizable groups, one of which ionizable groups is capable of forming an easily dissociative ionic salt, which salt can complex with the ionic functionality of the liposome-forming lipid. Papahadjopoulos exemplifies the use of buffers comprising histidine and TES, both of which appear to meet the definition of a “hydrating agent”. However, Papahadjopoulos did not require that the aqueous phase added to the lipids must be buffered, but only that it comprises the biological agent to be encapsulated. The inclusion or exclusion of a buffering agent in the aqueous phase is a matter of design choice, as is the selection of any particular buffering agent. It would have been obvious to one of ordinary skill in the art to either include in, or exclude from, the aqueous phase an ionizable agent such as a buffer. If one chose to include a buffer, it would have been obvious to use any known biological buffer, including monoionic buffers such as imidazole.

Regarding claim 146, Papahadjopoulos is silent as to the total amount of organic solvent remaining in the gel, but it is clear that this is a result-effective variable that is routinely optimized by one of ordinary skill. See e.g. column 4, lines 53-58.

Papahadjopoulos did not teach a water miscible organic solvent or N-acyl phosphatidylethanolamines.

Kikuchi taught that the use of volatile organic solvents for dissolution of lipids in methods of making liposomes was problematic because these organic solvents tend to remain in the final preparation and can be harmful to human health. Kikuchi suggests the use of water miscible organic solvents, such as ethylene glycol, for dissolution of lipids in methods of preparing liposomes. See column 1, line 60 to column 2, line 14; and column 2, lines 42-50. Kikuchi disclosed a number of acceptable organic solvents, including glycerol, ethylene glycol, and propylene glycol. Neither Papahadjopoulos nor Kikuchi specifically taught ethanol, methanol, or 2-propanol as water-miscible organic solvents.

Lenk taught a variety of solvents that cold be used to solubilize lipids, including ethanol, methanol, or 2-propanol. See table VI at column 40.

Thierry taught methods of making liposomes comprising lipid-nucleic acid complexes, wherein lipids are solubilized in an alcohol having 1-4 carbon atoms, preferably 2 to 3 (such as ethanol, isopropanol, glycerol, ethylene glycol, or propylene glycol), a nucleic acid is added to the lipids, and liposomes are formed comprising the nucleic acids. See Fig. 3; and column 8, lines 20-67). DNAs, RNAs, plasmids, antisense oligonucleotides, and ribozymes are examples of nucleic acids that can be

encapsulated. See paragraph bridging columns 6 and 7; column 9, lines 16-22; paragraph bridging columns 14 and 15; column 15, lines 51-58; and claim 29. Thierry also suggested the use of DOPE in the complexes. See e.g. column 5, lines 51-64.

Meers taught N-acyl phosphatidylethanolamines, including a N-dodecanoyl dioleoyl phosphatidylethanolamine, for use in liposome formation. See e.g. abstract; and column 4, lines 40-51. Meers also suggested the use of DOPE and DOPC in liposomes. See column 5, line 51 to column 6, line 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the water miscible solvent of Kikuchi in the method of Papahadjopoulos because Kikuchi taught that the use of water miscible organic solvents was safer for applications in which the product liposomes were to be used in vivo. It would have been similarly obvious to use the lipids of Meers in the liposomes of Papahadjopoulos because Meers suggested their use for liposome formation, and because N-dodecanoyl dioleoyl phosphatidylethanolamine and DOPE are fusogenic. See e.g. column 1, lines 48-60. Finally it would have been obvious to encapsulate plasmids or antisense oligonucleotides because this is suggested by Thierry.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use in the invention of Papahadjopoulos any water miscible organic solvent that can be used to solubilize liposome-forming lipids in view of the teachings of Kikuchi, as discussed above. It would have been obvious to use ethanol or 2-propanol because both Lenk and Thierry taught that these can be used to solubilize lipids. Note also that MPEP 2144.06 indicates that when it is recognized in the art that elements of an

invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. In this case it was clear that the glycerol, ethylene glycol, and propylene glycol of Kikuchi were art recognized equivalents of the ethanol and 2-propanol of Meers because each was disclosed as one of several alternative lipid solvents by Thierry.

Thus the invention as a whole was prima facie obvious.

Claims 18-24, 28, 32, 92-98, 101, 105, and 148-151 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos, Kikuchi, Meers, Lenk, and Thierry (US 6,096,335), as applied to claims 1-7, 10, 11, 13-17, 25-27, 29-31, 33, 34, 36-69, 71-80, 84-91, 99, 100, 102-104, 106, 107, 109-142, 144-147, and 153-168 above, and further in view of Eppstein et al (US Patent 4897355) taken with the evidence of GenBank Accession No. M77788.

The teachings of Papahadjopoulos, Kikuchi, Meers, Lenk, and Thierry are summarized above and render obvious methods of making liposomes comprising nucleic acids and N-acyl phosphatidylethanolamine lipids by solubilizing liposome-forming lipids in a C_1-C_3 alcohol.

These references are silent as to the sizes of the plasmid DNAs and oligonucleotides, and as to transfection incubation temperature and in vivo administration of plasmids.

Eppstein taught that liposomes could be used to encapsulate and deliver to cells plasmid DNAs and oligonucleotides, including pSVCAT (5 kbp) and oligonucleotides of an average length of about 130 bp. See column 3, lines 56-59; column 8, lines 32-40 and 43-45; column 10, lines 56-59; column 48 lines 24-50, and paragraph bridging columns 48 and 49. GenBank Accession No. M77788 provides evidence that PSVCAT is 5003 base pairs in length.

Eppstein also taught a variety of lipids that could be used to form liposomes including dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine, and cholesterol (see paragraph bridging columns 7 and 8; column 16, lines 53-and 54; and column 38, line 37).

Eppstein also taught methods of transfecting eukaryotic cells in vitro at 37^{o}C (column 45, lines 43-52), as well as intravenous delivery to humans (see column 8, lines 1-13; column 10, lines 37-62; column 12, lines 48-53; column 13, lines 27-29; and column 20, lines 21-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Papahadjopoulos as modified by Kikuchi, Meers, Lenk, and Thierry to encapsulate the plasmid or oligonucleotides of Eppstein because Papahadjopoulos suggests that the liposomes will protect nucleic acids from degradation (see e.g. column 13, lines 59-67), and because one of ordinary skill would

clearly appreciate their utility for this purpose in view of the teachings of Eppstein. It would have been similarly obvious to use the lipids of Eppstein in the methods of Papahadjopoulos, because MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. In this case the lipids of Eppstein are clearly suitable for making liposomes. Finally it would have been obvious to use the liposomes to transfect eukaryotic cells in vitro or in vivo, as well as for intravenous delivery in humans because this was suggested by Eppstein.

Response to Arguments

Applicant's arguments filed 3/16/09 have been fully considered but they are not persuasive.

Applicant argues at pages 21-23 of the response that one of ordinary skill would not have substituted a water miscible solvent of Kikuchi for the water immiscible solvent of Papahadjopoulos because Papahadjopoulos requires the use of a water immiscible organic solvent for forming inverted micelles. An aqueous mixture containing the biologically active agent is added to the inverted micelles to form an emulsion, and upon removal of the organic solvent, the inverted micelles revert to a bilayer-like structure to form large oligolamellar vesicles. Applicant argues that one would have had no reasonable expectation of success in using a C1-C3 alcohol instead of a water immiscible solvent, particularly in view of column 6, lines 56-61, which indicate that emulsification of the initial aqueous phase into the organic phase, and removal of the

organic phase prior to addition of any further aqueous phase is essential for high capture efficiency, and is a critical difference between the new process and previous processes.

The Examiner agrees that Papahadjopoulos indicated the importance of forming inverted micelles in an emulsion of a water immiscible solvent and an aqueous phase. However, it is also clear that those of ordinary skill in the art understood that this was not necessary for encapsulation of nucleic acids into liposomes, and that less toxic organic solvents could be used to dissolve lipids, such as those suggested by Kikuchi or Lenk. Note that Kikuchi taught methods of making liposomes by dissolving lipids in organic solvents to produce a liquid, paste, or gel, adding an aqueous phase comprising a nucleic acid, and stirring to form liposomes comprising the nucleic acid. Kikuchi found that homogeneous liposomes can be obtained with ease and good reproducibility when membrane components forming liposomes are dissolved or swollen in a water-soluble and physiologically acceptable non-volatile organic solvent and the resulting mixture is further mixed and stirred with an aqueous medium. See column 1, line 62 to column 2, line 2. There is no evidence of record that use of a water miscible solvent in the method of Papahadjopoulos would render the method inoperative. Based on the teachings of Papahadjopoulos cited by Applicant, one might expect to see a decrease in encapsulation yield, but this is not evidence of inoperability. Further, in performing the substitution, one would gain the advantage of eliminating from the final product organic solvents that are harmful to human health, as taught by Kikuchi. Accordingly, there is a rational basis for substituting the water miscible solvent for the water immiscible solvent.

In view of these teachings, and the teachings of Lenk and Thierry that lipids could be dissolved in C_1-C_3 alcohols, one of ordinary skill would clearly have had a reasonable expectation of success in using C_1-C_3 alcohols as an organic solvent in the methods of either Papahadjopoulos of Kikuchi. One would have realized that formation of an emulsion is not required for encapsulation, and that the use of toxic organic solvents could be avoided.

Applicant also argues that one of ordinary skill would not have used C_1-C_3 alcohols as an organic solvent because one appreciates that nucleic acids are not soluble in these solvents, relying for support on passages from "Molecular Cloning: A Laboratory Manual. However, this reference clearly teaches that the precipitation of nucleic acids in alcohols is performed with the addition of salt solutions. These salts decrease the solubility of the nucleic acid in water, and facilitate precipitation. The cited art does not teach the addition of salts that would decrease the solubility of nucleic acids such that they would precipitate in C_1-C_3 alcohols. The art cited by Applicant also teaches the use of at 2-3 volumes of alcohol for precipitation from a given volume of aqueous nucleic acid solution, whereas Kikuchi indicates that water miscible organic solvents can be used at about 0.001 to about 2 parts by weight per part by weight of the aqueous medium. Accordingly, one would have had reason to use a volume of alcohol that was less than what is generally used to precipitate nucleic acids, e.g. about 0.001 to about 2 parts by weight per part by weight of the aqueous medium. Finally, Thierry provides objective evidence that one of ordinary skill in the art prior to the invention

could have used the claimed alcohols in combination with nucleic acids to form liposomes encapsulating the nucleic acids. See e.g. Example 6 at column 13.

Applicant also asserts that one would not have used C_1-C_3 alcohols as a solvent because Kikuchi emphasizes the use of non-volatile organic solvents in contrast to the C_1-C_3 alcohols of the instant claims. This is unpersuasive because Kikuchi also emphasizes the concept of replacing toxic solvents with water soluble non-toxic solvents. Furthermore, the Thierry showed that C_1-C_3 alcohols were useful for solubilizing lipids for the formation of liposomes encapsulating nucleic acids, As discussed above.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635